ASSESSMENT OF PROGNOSTIC VARIABLES IN RCC – A PROSPECTIVE OBSERVATIONAL STUDY

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CERTIFICATE

This is to certify that this dissertation entitled **"ASSESSMENT OF PROGNOSTIC VARIABLES IN RCC – A PROSPECTIVE OBSERVATIONAL STUDY"** is a bonafide record of the research work done by **Dr.W.HARRY SANTHA SEELAN,** for the award of M.Ch., Genitourinary surgery, under the supervision of **Prof. R. JEYARAMAN, M.S. M.Ch.,** Professor & HOD, Dept. Of Urology, Government Madras Medical College, Chennai.

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DECLARATION

I solemnly declare that this dissertation ***"ASSESSMENT OF PROGNOSTIC VARIABLES IN RCC – A PROSPECTIVE OBSERVATIONAL STUDY"*** was prepared by me in the Department of Urology, Government Madras Medical College and Hospital, Chennai under the guidance &supervision of **Prof.R.JEYARAMAN,M.S. MCh.,** Professor &Head of the Department, Department of Urology, Government Madras Medical College, Chennai

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CONTENTS

INTRODUCTION

Renal cell carcinoma is the most frequently occurring solid lesion within the kidney and comprises different RCC types with specific histopathological and genetic characteristics (1). There is a 1.5:1 predominance of men over women, with peak incidence occurring between 60 and 70 years of age. Renal cell carcinoma represents 2-3% of all cancers is the most lethal of the urologic cancers

This is primarily a disease of the elderly patient, with typical presentation in the sixth and seventh decades of life (Pantuck et al, 2001). The worldwide and European annual increase in incidence is approximately 2%,(3) with approximately 30,000 new cases expected per year in the U.S. and 20,000 cases expected in the European Union, with a relative increase of 30% in the past 2 decades. Marked international variation in incidence exists being high in Northern Europe and North America and low in Asia, Africa and South America [Waterhouse et al].

In India RCC incidence is 3 per 100000 in males and 2.1 per 100000 in females per year. The incidence rate approaches 200,000 per year worldwide. The incidence of RCC has increased since the 1970s by an average of 3% per year for whites and 4% per year for African Americans, largely related to the more prevalent use of ultrasonography and CT scan for the evaluation of a variety of abdominal or gastrointestinal complaints (Chow et al, 1999).

Surgical resection of the involved kidney is by far the most successful intervention for localized RCC, yet at diagnosis, nearly 30% of patients present with metastatic disease. Despite intense surgical efforts, 30% to 40% of patients with no evidence of metastasis at time of surgery will subsequently develop distant metastasis. Eventually, 50% to 60% of all RCC patients develop metastatic disease. The 5-year survival rate for RCC patients with stage IV metastatic disease is a dismal 10%. Current methods for surveillance of disease progression after surgery are based entirely on clinical and Pathologic indices and do not incorporate molecular markers from tumor tissues.

Important predictors of outcome for RCC include tumor stage, Fuhrman nuclear grade, histopathological classification and peri operative thrombocytosis. Patient performance status using the ECOG classification system has been independently linked to outcome in patients with RCC, and figures prominently in the UISS nomogram from UCLA. The presence of local or systemic tumor symptoms have also been shown to be an independent predictor of patient outcome. There is no single prognostic variable which determines the recurrence. So we have done this study to find out if microvascular invasion can be considered as the most important prognostic variable predicting recurrence.

AIM OF THE STUDY

To evaluate the importance of various prognostic factors which determine the recurrence in RCC following radical nephrectomy and find out if microvascular invasion in tumors can turn out to be the most important prognostic variable of all the established prognostic variables.

REVIEW OF LITERATURE

The wide spread use of imaging in current medical practice has lead to an increased diagnosis of incidental renal tumors. However the incidentalomas represent 50% of RCCs diagnosed. And 20-40% develop metastases after nephrectomy for localized disease. Etiological factors include lifestyle factors, such as smoking, obesity and antihypertensive therapy (4, 5, 6). Cigarette smoking is a definite risk factor for RCC.

The roles of obesity and prolonged intake of antihypertensive medication as risk factors for RCC remain to be definitively clarified (7). The most effective prophylaxis is to avoid cigarette smoking. The most important primary prevention for RCC is to eliminate cigarette smoking and to avoid obesity (8, 9, 10). Although a number of potential etiologic factors have been identified in animal models, including viruses, lead compounds, and more than 100 chemicals such as aromatic hydrocarbons, no specific agent has been definitively established as causative in human RCC (Kantor, 1977). The majority of cases of RCC are believed to be sporadic; the National Cancer Institute estimates that only 4% are familial. Von Hippel–Lindau, Hereditary papillary RCC, Familial leiomyomatosis and RCC, Birt-Hogg-Dube syndrome.

PATHOLOGY

Most RCCs are round to ovoid and circumscribed by a pseudocapsule of compressed parenchyma and fibrous tissue rather than a true histologic capsule. Unlike upper tract transitional cell carcinomas, most RCCs are not grossly infiltrative, with the notable exception of collecting duct RCC and some sarcomatoid variant (Farrow, 1997). Tumor size has ranged from 5 to 8 cm in most series but can vary from a few millimeters to large enough to fill the entire abdomen. . When they are bivalved, RCCs consist of yellow, tan, or brown tumor interspersed with fibrotic, necrotic, or hemorrhagic areas; few are uniform in gross appearance.

Cystic degeneration is found in 10% to 25% of RCCs and appears to be associated with a better prognosis compared with purely solid RCC (Imura et al, 2004). Calcification can be stippled or plaque like and is found in 10% to 20% of RCCs. Nuclear features can be highly variable, and a number of grading systems have been based on such features as nuclear size and shape and the presence or absence of prominent nucleoli(11,18). Fuhrman's system has been most generally adopted and is now recognized as an important independent prognostic factor for (Fuhrman et al, 1982). Frank invasion and perforation of the collecting

system or renal capsule are found in approximately 20% of cases, although displacement of these structures is a more common finding. Further spread to involve adjacent organs is often precluded by Gerota's fascia acting as a barrier. One unique feature of RCC is its predilection for involvement of the venous system, which is found in 10% of RCCs, more often than in any other tumor type This is most commonly manifested in the form of a contiguous tumor thrombus that can extend into the inferior vena cava as high as the right atrium. Many such tumor thrombi are highly vascularised by arterial blood flow (Novick et al, 1990). Most sporadic RCCs are unilateral and unifocal. Bilateral involvement can be synchronous or asynchronous and is found in 2% to 4% of sporadic RCCs, although it is considerably more common in patients with Von Hippel–Lindau disease or other familial forms of RCC (Linehan et al, 2003). Multicentricity, which is found in 10% to 20% of cases, is more common in association with papillary histology and familial RCC.

Satellite lesions are often small and difficult to identify by preoperative imaging, intraoperative ultrasonography, or visual inspection; they appear to be the main factor contributing to local recurrence after partial nephrectomy. All RCCs are, by definition, adenocarcinomas, derived from renal tubular epithelial cells Most RCCs

share ultrastructural features, such as surface microvilli and complex intracellular junctions, with normal proximal tubular cells, and they are believed to be derived from this region of the nephron (11, 12). But it is not the case in other pathological types of RCCs which are believed to arise from other parts of nephron. Conventional RCC accounts for approximately 70% to 80% of all RCCs, representing the garden variety of RCC (Störkel et al, 1997). These tumors are typically yellow when they are bivalved and are highly vascular, containing a network of delicate vascular sinusoids interspersed between sheets or acini of tumor. On microscopic examination, common or conventional RCC can include clear cell, granular cell, or mixed types. Clear cells are typically round or polygonal with abundant cytoplasm containing glycogen, cholesterol, cholesterol esters, and phospholipids, all of which are readily extracted by the solvents used in routine histologic preparations, contributing to the clear appearance of the tumor cells (Farrow, 1997). However, granular cells, which have eosinophilic cytoplasm and abundant mitochondria, can predominate. Two percent to 5% of conventional RCCs also demonstrate sarcomatoid features, and conventional RCC is more likely to exhibit venous tumor extension than is any other subtype of RCC (Rabbani et al, 2004).

In general, patients with conventional RCC have a worse prognosis compared with chromophilic or chromophobic RCC, even after stratification for stage and grade (Cheville et al, 2003; Beck et al, 2004). However, most responders in immunotherapy protocols have had conventional RCC, and these protocols are now being reserved primarily for this population (Childs et al 2000; Drachenberg and Childs, 2003). Chromosome 3 alterations and *VHL* mutations are common in conventional RCC, and mutation or inactivation of this gene has been found in a majority of sporadic cases (Linehan et al, 2003). Chromophilic RCC, which has also been designated papillary RCC in other classification schemes, is the second most common histologic subtype (Störkel et al, 1997). It represents 10% to 15% of all RCCs, although it is more commonly found in certain populations, such as patients with end-stage renal failure and acquired renal cystic disease (Störkel et al, 1997). On microscopic examination, most tumors in this category consist of basophilic or eosinophilic cells arranged in papillary or tubular configuration. The cytogenetic abnormalities associated with chromophilic RCC are characteristic and include trisomy of chromosomes 7 and 17 and loss of the Y chromosome (13, 14,)

Another unique feature of chromophilic RCC is its tendency toward multicentricity, which approaches 40% in many series (Chow et

al, 2001).At present, many authors believe that grade for grade and stage for stage, a significant difference in outcome for patients with chromophilic RCC versus conventional RCC may be difficult to demonstrate (Renshaw, 2002). Chromophobe cell carcinoma is a distinctive histologic subtype of RCC that appears to be derived from the cortical portion of the collecting duct (Störkel et al, 1997). It represents 3% to 5% of all RCCs (Oyasu, 1998). The tumor cells typically exhibit a relatively transparent cytoplasm with a fine reticular pattern that has been described as a "plant cell" appearance. A perinuclear halo is typically found, and electron microscopic findings consist of numerous 150- to 300-nm microvesicles, which are the single most distinctive and defining feature of chromophobe cell carcinoma (Krishnan and Truong, 2002). Collecting duct or Bellini's duct, carcinoma is a relatively rare subtype of RCC, accounting for less than 1% of all RCCs. Many reported cases have occurred in younger patients, often in the third, fourth, or fifth decade of life (Carter et al, 1992). Collecting duct carcinomas are derived from the medulla, but many are infiltrative, and extension into the cortex is common (Pickhardt et al, 2001).

On microscopic examination, these tumors consist of an admixture of dilated tubules and papillary structures typically lined by a single layer of cuboidal cells, often creating a cobblestone appearance. Renal

medullary carcinoma is a relatively new subtype of RCC that occurs almost exclusively in association with the sickle cell trait. It is typically diagnosed in young African Americans, often in the third decade of life (Swartz et al, 2002). Renal medullary carcinoma is thought to arise from the calyceal epithelium near the renal papillae but is often highly infiltrative (Davis et al, 1995). Many cases are both locally advanced and metastatic at the time of diagnosis. Most patients do not respond to therapy and succumb to their disease in a few to several months (Polascik et al, 2002). The site of origin (renal papillae) and association with sickle cell trait suggest that a relatively hypoxic environment may contribute to tumorigenesis.

DIAGNOSIS AND STAGING

Due to the increased detection of tumours by the use of imaging techniques such as ultrasound and Computerized tomography (CT), an increasing number of incidentally diagnosed RCCs are found. These tumours are more often smaller and of low stage (8-10). Despite the increased incidental detection rate, the mortality from RCC has remained unaffected and parallel to the incidence. Many renal masses remain asymptomatic and non- palpable until late in the natural course of the disease today, more than 50% of RCCs are detected incidentally using

non-invasive imaging for the evaluation of a variety of non-specific symptom complexes (17, 19).

The classic triad of flank pain, gross haematuria and palpable abdominal mass is now rarely found in (6-10%). Paraneoplastic syndromes are found in around 30% of patients with symptomatic RCC (21, 23). The most common of these are, hypertension, cachexia, weight loss, pyrexia, neuromyopathy, amyloidosis, elevated erythrocyte sedimentation rate, anaemia, abnormal liver function, hypercalcaemia, polycythaemia, etc, (20-22).

A minority of patients present with symptoms directly caused by metastatic disease, such as bone pain or persistent cough (1). Still, 25-30% of patients are diagnosed due to symptoms associated with metastatic disease. Physical examination has a limited role in diagnosing RCC, but it may be valuable in some cases such as palpable abdominal mass, palpable cervical lymphadenopathy, non-reducing varicocele or bilateral lower extremity oedema, which suggests venous involvement. These findings should initiate radiological examinations. The most commonly assessed laboratory parameters are haemoglobin, erythrocyte sedimentation rate, alkaline phosphatase and serum calcium (1, 4) .The staging system used is 2002 TNM system which gives idea about the

local, regional and systemic extent of tumor pre operatively. Tumors which are enhancing on contrast administration are taken as malignant and there is no role of pre operative biopsy as there is false negative rate of around 30% by conventional HPE methods. Since there is difficulty in differentiating benign and malignant neoplasm there is a role of fluorescent in situ hybridization (FISH) technique which has a sensitivity and specificity of more than 95% because it looks for the specific chromosomal abnormalities present in individual tumors.The local staging is assessed by seeing the size of the tumor and how the fat plane between the tumor and surrounding structures is maintained. Typical perinephric stranding is looked for which is due to the obstruction of lymphatics by the tumor cells. The presence of hilar, caval, inter aorto caval and para aortic nodes are looked for. The signs of venous involvement are looked for by seeing at the shape of IVC and any filling defect. The presence of metastasis is assessed by evaluating according to symptoms.

RADIOLOGICAL INVESTIGATIONS

The majority of renal tumours are diagnosed by abdominal ultrasound (US) and CT performed for various reasons (24, 25). Detection of a solid renal mass with US should be further investigated

with a high-quality CT scan using contrast medium (26, 32). It serves to verify the diagnosis of RCC and provides information on the function and morphology of the contralateral kidney.

Abdominal CT assesses primary tumour extension with extrarenal spread and provides information on venous involvement, enlargement of locoregional lymph nodes, and condition of adrenal glands and the liver (27, 29). Chest CT is the most accurate investigation for chest staging (28), but at least routine chest radiography, as a less accurate alternative, must be done for metastatic evaluation. A plain chest X-ray can be sufficient for assessment of the lung in low-risk patients but chest CT is most sensitive (30, 31).

Magnetic resonance imaging (MRI) can be reserved primarily for patients with locally advanced malignancy, possible venous involvement, renal insufficiency or allergy to intravenous contrast (34-35). Magnetic resonance imaging is also an option for the evaluation of inferior vena cava tumour thrombus extension and the evaluation of unclassified renal masses (36-38).

Evaluation of the tumour thrombus can also be performed with Doppler US in such cases. There is consensus that most bone and brain metastases are symptomatic

At the time of diagnosis and that routine bone scan or brain CT are not generally indicated (40). In high-risk patients for bone metastases (raised alkaline phosphatase or bone pain), further evaluation utilizing an imaging approach should be done (39), if indicated by clinical or laboratory signs and symptoms,

Other diagnostic procedures may be applied, such as bone scan (41), brain CT or MRI. Renal arteriography, inferior venacavography or fine-needle biopsy. Have only a limited role in the clinical work-up of patients with RCC, but may be considered in selected cases.

Routine evaluation by doing all the available modalities is not necessary because it adds to the cost and does not help in the management. By CT if typical >20 HU enhancement is made out and there is tumor deenhancement which is characteristic of RCC which is due to the lack of functioning tubules and increased neo vascularity due to VEGF production especially in clear cell RCC it virtually confirms the diagnosis .

In certain situations when there is a central hilar tumor it is difficult to differentiate from collecting system tumors. In these cases we have to look for distortion of renal out line due to exophytic growth of tumor and neo vascularity which is due to increased growth factors. Usually

collecting system tumors are infiltative in nature and they don't produce a palpable mass. They are also less vascular than RCC due to absence of VEGF production.

PROGNOSTIC FACTORS

The 2002 TNM stage classification system is generally recommended for clinical and scientific use. It is unclear whether the current TNM classification is optimal for the prediction of survival in patients with RCC and might be a subject for re-classification. The pT1 substratification, introduced in 2002 (1), has been validated by a number of studies (2-4) However, refinements remain to be performed for pT3 tumours

Firstly, for renal sinus fat invasion only,it has not been established whether this carries the same prognostic information as does perinephric fat invasion . Secondly, many studies have suggested that adrenal invasion represents a very poor prognosticgroup.It has been suggested that these RCCs should be classified as T4 tumours . Furthermore, it is still not clearwhether the stratification of RCCs with venous invasion in T3b and T3c is accurate. Additional studies arerequired to investigate the independent prognostic value of vena caval invasion compared with renal vein invasion. More recently, the accuracy of the N1-N2subclassification

has been questioned. For adequate M-staging of patients with RCC, an accurate pre-operative imaging procedure, which is currently chest and abdominal CT, should be performed. Factors influencing prognosis can be classified into: **anatomical, histological, clinical and molecular**.

Anatomical factors

Anatomical factors include tumour size, venous invasion, renal capsule invasion, adrenal involvement, and lymph node and distant metastasis. Overall, tumor-related factors such as pathologic stage, tumor size, nuclear grade, and histologic subtype have the greatest utility on an independent basis. However, an integrative approach, combining a variety of factors that have proved to have independent value on multivariate analysis, appears to be most powerful. (Kontak and Campbell, 2003).

Giuliani and colleagues (1990) reported 5-year survival rates of 84% for patients with tumor diameter less than 5 cm, 50% for tumors between 5 and 10 cm, and 0% for tumors more than 10 cm in diameter. To a large extent, this is due to a strong correlation between tumor size and pathologic tumor stage. Guinan and coworkers (1995b) have also shown that tumor size can function as an independent prognostic factor.

Frank and colleagues (2003a) have shown that larger tumors are more likely to exhibit clear cell histology and high nuclear grade, and both of these factors correlate with a compromised prognosis. A review of 1771 patients with organ-confined RCC showed 10-year cancer-specific survival rates of 90% to 95%, 80% to 85%, and 75% for patients with pT1a, pT1b, and pT2 tumor, respectively (Patard et al, 2004a). Other studies have also shown a particularly favorable prognosis for the unilateral pT1a tumors that are now being discovered with increased frequency. In series from the Cleveland Clinic and the Mayo Clinic, such tumors were associated with greater than 95% 5-year survival rates, whether they were managed by nephron-sparing surgery or radical nephrectomy(Cheville et al).

Histological factors

Pathologic stage has proved to be the single most important prognostic factor for RCC (Kontak and Campbell, 2003). The extent of loco-regional or systemic disease at diagnosis is the primary determinant of outcome for this disease (Bassil et al, 1985). These studies demonstrate 5-year survival rates of 70% to 90% for organ-confined disease and document a 15% to 20% reduction in survival associated with invasion of the perinephric fat (Leibovich et al, 2005). Renal sinus

involvement should definitely be classified as T3a, and studies suggest that these patients may be at higher risk for metastasis related to increased access to the venous system (Bonsib et al, 2000; Uzzo et al, 2002).

Several reports have shown that most patients with ipsilateral adrenal involvement, which is found in 1% to 2% of cases, eventually succumb to systemic disease progression, suggesting a hematogenous route of dissemination or a highly invasive phenotype (von Knobloch et al, 2004; Siemer et al, 2005; Thompson et al, 2005). Venous involvement was once thought to be a poor prognostic finding for RCC, but several reports demonstrate that many patients with tumor thrombi can be salvaged with an aggressive surgical approach. These studies document 45% to 69% 5-year survival rates for patients with venous tumor thrombi as long as the tumor is otherwise confined to the kidney. Golimbu and associates (1986) reported 84% 5-year survival in the best of circumstances—tumor thrombus limited to the main renal vein and tumor otherwise confined to the kidney.

Patients with venous tumor thrombi and concomitant lymph node or systemic metastases have markedly decreased survival, and those with tumor extending into the perinephric fat have intermediate survival (Gettman et al, 1999 ; Naitoh et al, 1999 ; Bissada et al, 2003 ;

Moinzadeh and Libertino, 2004 ;). The importance of tumor invasion into the perinephric fat and its negative impact on prognosis for patients with tumor thrombi is highlighted in the series by Leibovich. The prognostic significance of the cephalad extent of tumor thrombus has been controversial, and it is difficult to compare various series because of differences in selection of patients and related covariables (Leibovich et al, 2005).

However, data suggest that the cephalad extent of tumor thrombus is not of prognostic significance as long as the tumor is otherwise confined Direct invasion of the wall of the vein appears to be a more important prognostic factor than cephalad extent of tumor thrombus and should be noted during tumor staging. Hatcher and colleagues (1991) reported 69% 5-year survival when the wall of the vein was clean, which was reduced to 25% when direct invasion of the caval wall was observed.

Eastern Cooperative Oncology Group performance status, metastatic status, sarcomatoid features and concomitant perinephric fat invasion are the most powerful prognostic factors of survival in renal cell carcinoma with tumor thrombus extension. (Klatte et al) .The major drop in prognosis comes in patients whose tumor extends beyond Gerota's fascia to involve contiguous organs, which is rarely associated with 5-

year survival, and in patients with lymph node or systemic metastases (Thrasher and Paulson, 1993).

Lymph node involvement has long been recognized as a dire prognostic sign because it is associated with 5- and 10-year survival rates of 5% to 30% and 0% to 5%, respectively (Bassil et al, 1985 ; Phillips and Taneja, 2004). Median survival at follow up was 49 months. Five-year cancer specific survival was 60% for pT3a, 46.2% for pT3b, 10% for pT3c and 12% for pT4 tumours ($p < 0.0001$).

According to median survival, the authors identified 3 prognostic groups, including GROUP 1-patients with renal vein thrombosis (117 months), fat invasion (98 months) or infradiaphragmatic vena caval thrombosis (67 months), GROUP 2-patients with adrenal invasion alone (24 months), renal vein thrombosis plus fat invasion (24 months) or infradiaphragmatic vena cava plus fat invasion (24 months) GROUP 3-patients with renal or infradiaphragmatic caval thrombosis plus adrenal involvement (11 months), supradiaphragmatic vena caval thrombosis (12 months) or Gerota's fascia invasion (12 months).

Five-year cancer specific survival rates in groups 1 to 3 were 61%, 35% and 12.9%, respectively ($p < 0.0001$). On multivariate analysis the proposed classification had an independent prognostic value. Ficarra et

al. (2007) provide an adequate prognostic stratification for locally advanced renal cell carcinoma and propose a new TNM classification concluded that the results suggest the necessity of reclassifying locally advanced renal cell carcinoma according to the 3 described prognostic categories.

Systemic metastases portend a particularly poor prognosis for RCC, with 1-year survival of less than 50%, 5-year survival of 5% to 30%, and 10-year survival of 0% to 5% (Negrier et al, 2002; Sella et al, 2003). The statistics for patients presenting with synchronous metastases are even worse, with most patients dying of disease progression within a year. For patients with asynchronous metastases, the metastasis-free interval has proved to be a useful prognosticator becauseit reflects the tempo of disease progression (Negrier et al, 2002).

Other important prognostic factors for patients with systemic metastases include performance status, number and sites of metastases, anemia, hypercalcemia, elevated alkaline phosphatase or lactate dehydrogenase levels, and sarcomatoid histology (Motzer et al,2004). Visceral metastases have been associated with a particularly poor prognosis, in contrast to pulmonary-only disease, (Negrier et al, 2002). Bulky retroperitoneal lymphadenopathis now also established as a strong

negative prognostic factor in patients with metastaticRCC (Vasselli et al, 2001; Pantuck et al, 2003a,). Prior nephrectomy has correlated with improved survival and cytoreductive nephrectomy may provide a modest survival benefit, although the mechanism for this is under debate (Flanigan et al, 2001).

Multivariate analysis identified the following independent adverse prognostic factors(PF)for progression free survival in advanced RCC

(1) time from diagnosis to current treatment < 2 years

(2) baseline platelet count > 300,000 cells/microliter (mcL)

(3) baseline neutrophil count > 4500 cells/mcL

(4) baseline corrected serum calcium < 8.5 or > 10.0 mg/dL; and

(5) initial ECOG performance status (PS) > 0.

Using these factors, 3 prognostic subgroups were identified based on the number of adverse PFs presents. Median PFS in patients with 0 or 1 adverse PFs was 20.1 months (95% CI, 19.0-22.3) compared with 13 months (95% CI, 8.6-17.6) in patients with 2 adverse PFs and 3.9 months (95% CI, 1.8-7.2) in patients with more than 2 adverse PFs. A nomogram was created to estimate the likelihood of PFS of 12 or more months with

corrected calcium, PS, nephrectomy, lactate dehydrogenase, thrombocytosis, number of metastatic sites, and time from diagnosis to treatment.

Other important prognostic factors for RCC include nuclear grade and histologic subtype. Renal tumor classification is important because histopathological subtypes are associated with distinct clinical behavior. However, diagnosis is difficult because tumor subtypes have overlapping microscopic characteristics. Clear cell RCC overexpressed proximal nephron, angiogenic, and immune response genes, chromophobe RCC oncocytoma overexpressed distal nephron and oxidative phosphorylation genes, papillary RCC overexpressed serine protease inhibitors, and extracellular matrix products, and angiomyolipoma overexpressed muscle developmental, lipid biosynthetic, melanocytic, and distinct angiogenic factors.

Quantitative reverse transcriptase-polymerase chain reaction and immunohistochemistry of formalin-fixed renal tumors confirmed overexpression of proximal nephron markers (megalin/low-density lipoprotein-related protein 2, α-methylacyl CoA racemase) in clear cell and papillary RCC and distal nephron markers (β-defensin 1, claudin 7) in chromophobe RCC/oncocytoma.

Histopathological subtypes of renal neoplasms expressed distinct, biologically relevant molecular signatures. For example, clear cell RCC was revealed as an immunogenic and angiogenic tumor related to proximal nephron epithelium. Chromophobe RCC and oncocytoma appeared to be closely related neoplasms, overexpressing distal nephron markers and energy pathway genes, and underexpressing IκB kinase/nuclear factor-κB regulators and cell death genes. Papillary RCC expressed a distinct molecular signature, including serine protease inhibitors, extracellular matrix products, and proximal nephron markers such as *AMACR*. Angiomyolipoma was characterized as a mesenchymal tumor with adipose, smooth muscle, vascular, and melanocytic features.

Several grading systems for RCC have been proposed on the basis of nuclear size and morphology and presence or absence of nucleoli. Nuclear grade has proved in many cases to be an independent prognostic factor when it is subjected to multivariate analysis (Patard etal).

In North America, Fuhrman's classification system has been most generally adopted. In Fuhrman's original report, the 5-year survival rates for grades 1 to 4 were 64%, 34%, 31%, and 10%, respectively, and nuclear grade proved to be the most significant prognostic factor for stage I tumors in this series (Fuhrman et al, 1982). In most series, prognostic

significance has been found primarily at the ends of the spectrum given the difficulties of distinguishing the intermediate grades; a consensus conference on tumor grading for RCC recommended changing to a three-tiered system.

Histologic subtype can also carry prognostic significance, although, again, primarily at the ends of the spectrum. The presence of sarcomatoid differentiation or collecting duct or medullary cell histologic subtype denotes a poor prognosis (Polascik et al, 2002).

Estimates of DNA ploidy and assessment of nuclear morphometry have also correlated with outcomes for patients with RCC, but the main utility of ploidy appears to be inpatients with organ-confined disease, and the role of nuclear morphometry has not been defined.

Clinical factors

Clinical factors include patient performance status, localized symptoms, cachexia, anaemia, platelet count. Anemia, thrombocytosis, hypercalcemia, albuminuria, elevated serum alkaline phosphatase, erythrocyte sedimentation rate, and other paraneoplastic signs or symptoms have also correlated with poor outcomes for patients with RCC (Symbas et al, 2000).

In the large population study led by Verhoest and colleagues from several European hospitals, the clinical parameters for four patient age groups were evaluated to determine the influence of age at diagnosis on tumor characteristics and outcomes for RCC. The authors concluded that age is indeed an independent prognostic variable for RCC clinical parameters and overall survival. Younger patients appear to have lower stage and grade tumors, and a higher incidence of more favorable histologic subtypes such as papillary and chromophobe. Age at diagnosis should be considered in counseling patients regarding outcomes, but this factor should await further prospective validation prior to widespread implementation in prognostic nomograms, because although there are some studies to show the younger age patients have papillary histology and good prognosis when compared to older individuals no concrete evidence is available in the studies available.

Molecular factors

There are numerous molecular markers being investigated including: carbonic anhydrase IX (CAIX), vascular endothelial growth factor (VEGF), hypoxia inducible factor (HIF), Ki67 (proliferation), p53, PTEN (cell cycle), Ecadherin, CD44 (cell adhesion) (55). As yet, these markers are not in wide spread use. Recently, gene expression profiling

has identified 259 genes, which predict survival independent of clinicalprognostic factors in conventional RCCs, indicating that genetic information will improve prognostication.

The most promising of molecular factor appears to be CA-9, which is regulated by the *VHL* gene and is over expressed in many conventional RCCs (Bui et al, 2003, 2004). High CA-9 expression has correlated with improved survival in this population, suggesting that tumors with *VHL*-independent pathogenesis may have increased aggressiveness. Decreased proliferative index as assessed by Ki-67 has also correlated with improved survival in clear cell RCC (Bui et al, 2004).

Other factors that may prove to be useful include apoptotic indices; genetic elements, such as *p53* (Shvarts et al, 2005); and evaluation of the expression and function of various growth factors and their receptors. Histopathological subtypes of renal neoplasms expressed distinct, biologically relevant molecular signatures. For example, clear cell RCC was revealed as an immunogenic and angiogenic tumor related to proximal nephron epithelium. Chromophobe RCC and oncocytoma appeared to be closely related neoplasms, overexpressing distal nephron markers and energy pathway genes, and underexpressing IκB kinase/nuclear factor-κB regulators and cell death genes. Papillary RCC

expressed a distinct molecular signature, including serine protease inhibitors, extracellular matrix products, and proximal nephron markers such as *AMACR*. Angiomyolipoma was characterized as a mesenchymal tumor with adipose, smooth muscle, vascular, and melanocytic features. Additional clinical or pathological properties may be revealed by further analysis of the microarray data and the case cohort. Consistent with various research results, microarray data could be translated into specific quantitative RT-PCR and immunohistochemical assays using formalin-fixed paraffin-embedded tissues, which may be applicable in clinical settings for diagnosis and clinical management of renal tumors.

Assays for the levels of proangiogenic factors such as VEGF or basic fibroblast growth factor in the serum or urine may also improve prognostication (Mizutani et al, 2003). Gene array and proteomic technology identify additional prognostic factors (Kim et al) . The active form of vitamin D3, that is 1alpha, 25-dihydroxyvitamin D3, binds with vitamin D receptor, which forms a complex with retinoid X receptors alpha, beta and gamma to manifest antitumor effects. Obara et al. (2007) examined the expression of vitamin D receptor and retinoid X receptors in renal cell carcinoma and elucidated the prognostic significance of these receptors. They examined immunohistochemically vitamin D receptor, and retinoid X receptors alpha, beta and gamma in

nephrectomized specimens of 68 patients with renal cell carcinoma.They analyzed the correlation between the expression of these receptors and clinicopathological parameters or patient survival. The 5-year cancer specific survival rate was higher in patients with retinoid X receptor gamma positive renal cell carcinoma than those with retinoid X receptor gamma negative renal cell carcinoma (79.3% vs 40.0%, $p < 0.05$). Significant correlation was observed between the expression of retinoid X receptor gamma and tumor stage, distant metastasis or the 5-year cancer specific survival rate.

Furthermore, retinoid X receptor gamma expression was an independent prognostic factor in patients with renal cell carcinoma. The importance of molecular factors is now slowly getting established and there many studies to prove their significance in recurrence. The importance of various molecular factors in influencing the recurrence is not specifically known so that it can be utilized in prognostic nomograms. At present there are no nomograms using this factors in predicting the recurrence but in future these factors will come to play in selecting the follow up protocol and in selecting the adjuvant therapy protocols. These need sophisticated methods of analysis but will be useful in predicting the biological behaviour of the tumor.

TREATMENT OF LOCALIZED DISEASE

Radical nephrectomy that includes the removal of the tumour-bearing kidney remains the gold standard curative therapy for patients with localized RCC and offers a reasonable chance of curing the disease (1).There is no evidence to favour a specific surgical approach. Except in the case of a large upper pole tumour, which is associated with a risk of direct invasion of the adrenal gland, or a tumour of > 7 cm maximum diameter, which is associated with a higher risk of intra-adrenal metastatic spread, there is evidence that a routine adrenalectomy is unnecessary during the surgical treatment of RCC, provided the pre-operative imaging procedures for tumour staging (CT, MRI) reveal negative findings.

Current evidence that adjuvant tumour vaccination might improve the duration of the progression-free survival of selected subgroups of patients undergoing nephrectomy for T3 renal carcinomas needs further confirmation regarding the impact on overall survival. Prognostic algorithms might identify patients likely to derive the largest clinical benefit from adjuvant vaccination therapy.

Adjuvant therapy with cytokines does not improve survival after nephrectomy Outside controlled clinical trials, there is no indication for

adjuvant therapy following surgery. There lot of molecular targeted therapies against tyrosine kinase, VEGF and other pathways which have some value in tumors with high chance of recurrence.

SURVEILLANCE FOLLOWING SURGERY

Surveillance after radical surgery allows the urologist to monitor or identify:

• Post-operative complications

• Renal function

• Local recurrence

• Recurrence in the contralateral kidney

• Development of metastases.

PROGNOSTIC SYSTEMS AND NOMOGRAMS

Prognostic systems and nomograms that combine independent prognostic factors have been recently developed. It has been suggested that these systems are more accurate than TNM stage or Fuhrman grade alone for predicting survival. In patients with RCC, TNM stage, nuclear grade according to Fuhrman and RCC subtype (WHO 2004) should be performed because they contribute important prognostic information.

There are currently no prognostic integrated systems or molecular markers recommended for routine clinical use. Several groups have constructed prognostic algorithms to facilitate clinical followup and identify patients for adjuvant treatment.

In 2001 the group at MSKCC proposed a nomogram for patients with localized clear cell, papillary and chromophobe RCC (63). Prognostic factors include tumor stage, tumor size, histological sub type and symptoms at presentation. A recently revised nomogram for patients with clear cell carcinoma from MSKCC includes tumor stage, tumor size, nuclear grade, necrosis, vascular invasion and symptoms at presentation as prognostic factors. Paper nomograms gives a visual aid to clinicians to use during patient counseling. The software based nomograms provide accurate prognostic information and may take even less time to use during doctor patient interactions.Researchers at other institution have proposed 2 additional post operative prognostic nomogram systems.

The UCLA integrated staging system UISS divide patients into 5 Groups shown to have difference in survival. Initially the UCLA group has evaluated many prognostic parameters including age gender race and smoking history, the UISS is based solely on tumor stage nuclear grade

and ECOG performance status. In a subsequent report the UISS was modified to identify patients with non-metastatic or metastatic disease at low intermediate or high risk of disease progression. This modified UISS has been validated in larger series of patients internally and externally.

A drawback of the UISS is that it does not predict the probability of failure for an individual patient and instead place individuals into low intermediate and high risk group, making information provide less meaningful for treatment decision making. Grouping heterogeneous patients in particular into a high risk group leads to placement of patients who will do poorly with some who may never experience a recurrence. In 2002 the group at Mayo clinic devised the SSIGN (65).Several investigators have now combined various prognostic factors, and this has greatly improved the predictive capacity (Cindolo et al, 2005). For instance, Kattan and colleagues (2001) have combined manner of presentation (incidental or local versus systemic symptoms), tumor histology, tumor size, and pathologic stage to develop a nomogram that predicts cancer-free survival after nephrectomy.

Tumor grade was not included in this analysis because its role for nonconventional RCC has not been clearly defined. A subsequent analysis from this same group focused only on patients with conventional

RCC and incorporated tumor grade, assessment of tumor necrosis, and vascular invasion to further improve prognostication (Sorbellini et al, 2005). A similar model for conventional RCC has also been proposed by Frank and colleagues (2002) , in this case incorporating 1997 TNM stage, tumor size, nuclear grade, and presence of tumor necrosis to predict recurrence and survival after radical nephrectomy (Sengupta et al, 2005).

A sophisticated multivariate analysis revealed three independent prognostic factors that were most robust for predicting outcomes, namely, TNM stage, performance status, and tumor grade (Zisman et al, 2001b).Prediction of survival of patients has proved to be powerful, and this approach has now been validated in an independent analysis of 4202 patients from eight academic centers (Patardetal, 2004c). Subsequent reports segregated patients with N0 M0 tumors from those with N+ or M1 tumors and provided separate analyses for each subgroup, and this should be even more useful for the practicing clinician (Zisman et al, 2002c).

Molecular factors such as staining for CA-9 and p53 and assessment of proliferation status with Ki-67 are now also being incorporated into algorithms to predict outcomes for patients with RCC (Kim et al, 2005).

For patients with clinically localized disease, Patard and colleagues (2004a) have shown that mode of presentation (incidental versus symptomatic) can be combined with tumor size to better stratify patients after primary surgical management.

They have proposed a novel staging system for organ-confined RCC:

T1a <4.0 cm and incidental T1b: <4.0 cm and symptomatic or >4.0 cm and incidental T2a: >4 to ≤7 cm and symptomatic T2b: >7 cm and symptomatic Cancer-specific mortality rates at 5 years of follow-up were 1.9%, 4.1%, 13.8%, and 23.7%, respectively, showing that this simple modification could potentially improve prognostication for this population of patients (Patard et al, 2004a). Improved prognostication such as this will help guide counseling and management of patients and is likely to stimulate a reassessment of the current staging protocols for RCC.Prognostic systems or nomograms can be useful for the stratified inclusion of patients into clinical trials

The use of integrated prognostic systems or nomograms is not routinely recommended, although these systems provide a rationale for a prognostic prediction useful for including patients in clinical trials. No molecular prognostic marker is currently recommended for utilization in the clinical routine.

MATERIALS AND METHODS

Between September 2005 and December 2007, 85 patients aged 43- 74years (mean 60yrs) referred as renal mass by incidental detection on evaluation of other diseases or clinically presenting as loin pain, haematuria or renal mass were further evaluated for RCC by CECT KUB. Any enhancing mass lesion in kidney was taken as renal cell carcinoma. All the patients were analysed regarding the presence or absence of symptoms such as mass, and paraneoplastic symptoms.

Laboratory investigations were done to detect the presence of paraneoplastic syndromes. Metastatic work included Doppler evaluation of renal veins and IVC and in selected cases MRI. Chest x-ray to rule out pulmonary metastasis and in selected cases chest CT done. Bone scan was done in cases presenting with bone pain or LFT showing raised alkaline phosphatase. CT brain was taken when patient's symptoms suggested brain metastasis. After confirming it is localized tumor without metastasis and with normal contralateral functioning kidney, radical nephrectomy was done. In patients with IVC thrombus IVC thrombectomy was done.12 cases had metastasis at presentation. Remaining 73 cases were either localized or locally advanced and non metastatic were managed by radical nephrectomy and proven by

histopathological examination as renal cell carcinoma were enrolled in a prospective observational study. 6 cases were of benign histology and were excluded from study.

All the specimens were subjected to histopathological examination by institute pathologist .All factors the size, pathological stage, sub type, capsular invasion, sinus invasion, microvascular invasion, venous thrombus, venous invasion, margin status and nodal status were looked for. Specimen was specifically looked for tumor cells within the vascular system, which denotes microvascular invasion.

FOLLOWUP- All patients were followed up with physical examination, serum chemistry, X -ray chest and CECT. This was done every 4 months in the 1^{st} year, every 6 months in the 2^{nd} year and annually thereafter. Univariate and Multivariate analyses were used to evaluate whether MVI was associated with disease free and cancer specific survival. Chi-square test was used to evaluate the association among the variables. Kaplan-Meier method was used to develop survival curves. Differences among them were analysed using log –rank test. Cox-regression analysis was used to identify the factor which independently determines the recurrence and progression to death. A p value of < 0.05 was taken as significant.

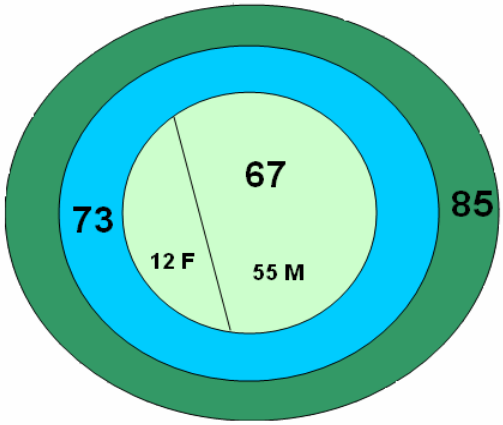
EXCLUSION CRITERIA

- Patients with metastatic disease at presentation
- Patients in whom radical nephrectomy is not done due to associated comorbid conditions
- Patients with CRF who develop RCC from Acquired Cystic Kidney Disease
- Patients who have undergone partial nephrectomy
- Patients with benign histopathological features
- Patients with bilateral tumors at presentation
- Patients with recurrence following partial nephrectomy
- Patients with inconclusive malignant histology
- Patients who developed post op medical complications and expired

RESULTS AND OBSERVATIONS

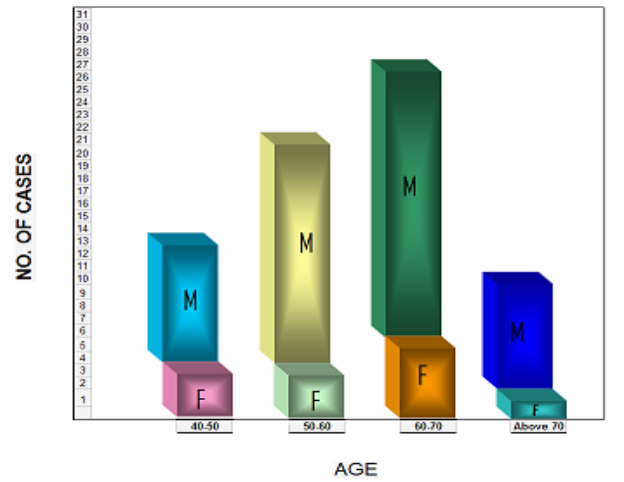
Patient Demographics

In our study there were totally 85 cases of renal mass who were evaluated of which 12 cases presenting with metastasis were excluded from the study. Of the remaining cases the final histology was benign in 6cases.On excluding these 6 cases only 67 cases were taken for the prospective observational study.



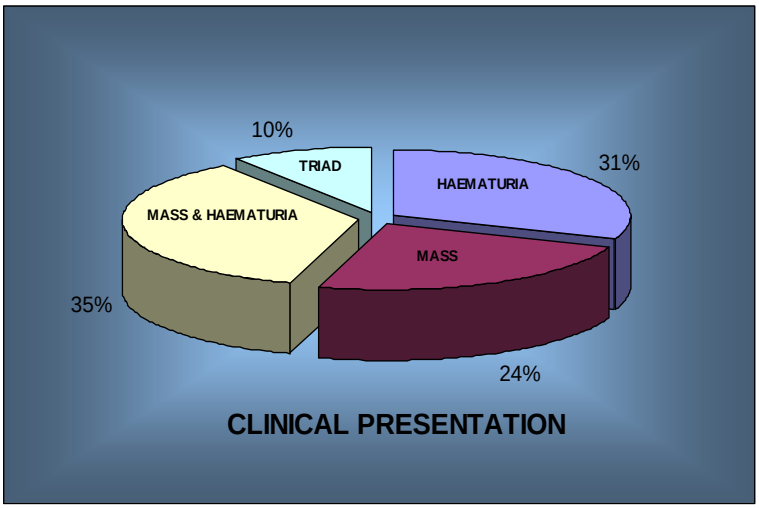
NO. OF CASES IN THE STUDY

Of the 67 patients 55 (82%) were males and 12 (18%) were females; the mean age was 60.3 yrs[43-74yrs] and the mean follow up was 21 [6-36] months. In our study the tumors were common in males when compared to females. The commonest age of presentation was 6th and 7th decade.



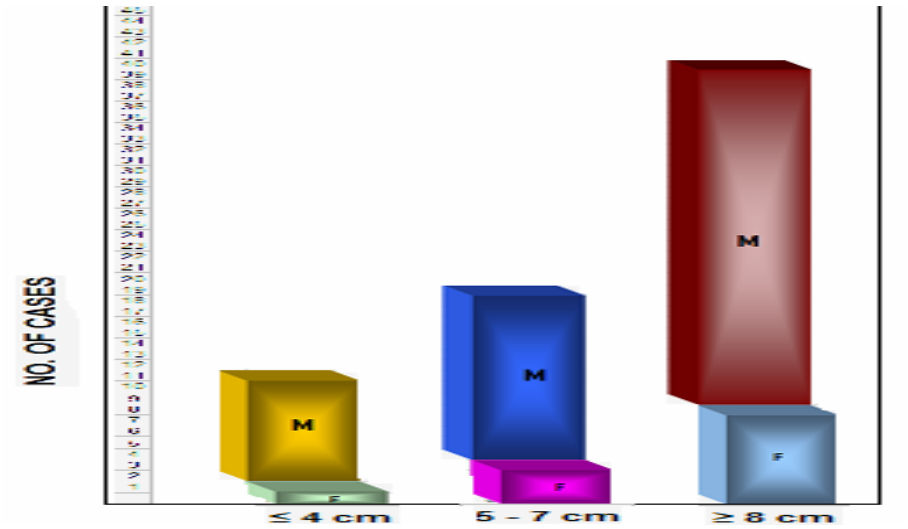
Clinical Presentation

At clinical presentation the tumor was incidental in 22(33%) and symptomatic in 45 (67%) with haematuria as the main presentation in 31% of patients, mass in 24% of patients, both the findings in 35% and the classical triad in 10% of patients. The performance status was good in all the cases.There was no paraneoplastic maniefestation.



Tumor Size

In our study majority of tumors were more than 7 cms in size. Tumors less than 4cms were around 22% in incidence. Presentation as mass and loin pain was more common in tumors more than 7cms size. Less than 4 cm size was usually asymptomatic in presentation.

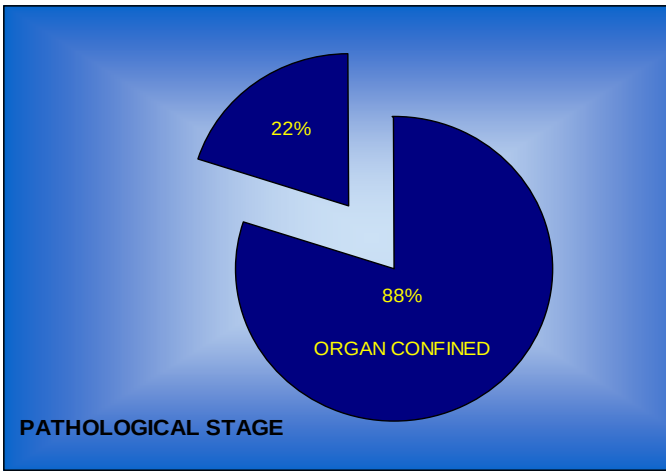


Histological Subtype

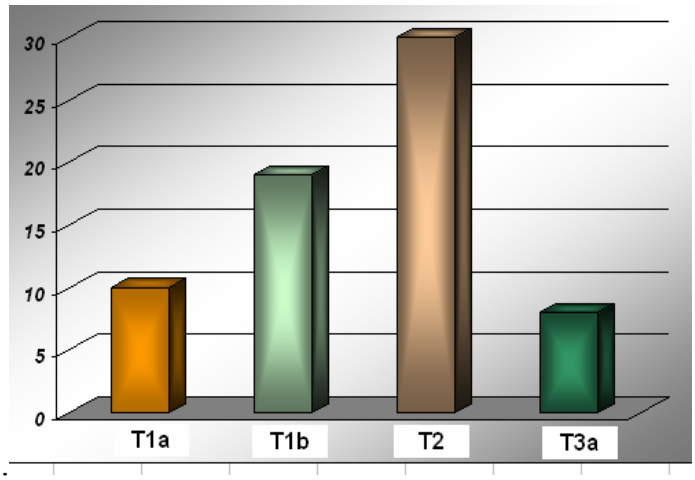
The distribution of histo pathological sub type was 90% clear cell carcinoma and those who had MVI all developed recurrence. In papillary tumors MVI was detected in one case that developed recurrence. We had one case of bellini duct carcinoma in our study.

Pathological Stage

In our study 88% of cases were organ confined and 12% were locally advanced. They had adrenal invasion or capsular invasion by HPE.

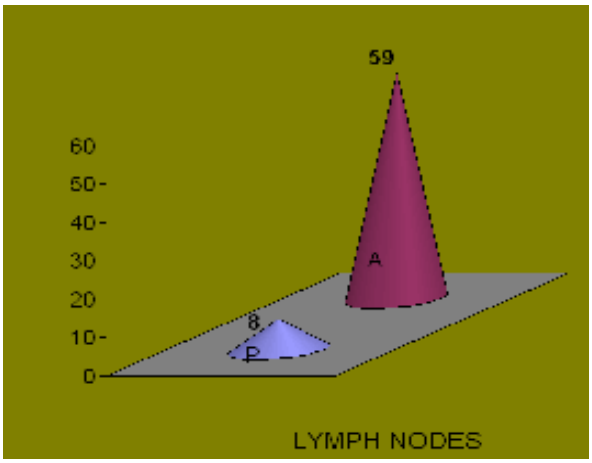


The commonest pathological stage was T2 and the incidence of tumor with stage T1a was around 14%.only 7% incidence of T3a tumors. These T2 tumors had higher incidence of MVI



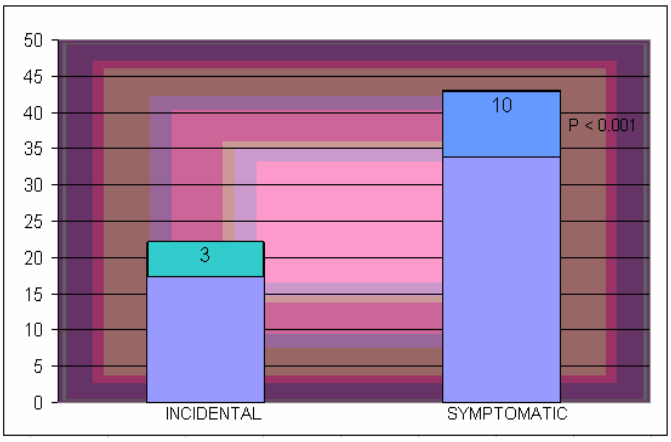
Lymph Node Status And Necrosis

Out of 8 positive lymph node cases 7 cases were MVI positive (p<.0001). Necrosis was present in 8% of our cases. The incidence was more in higher grade tumors.



MVI Incidence

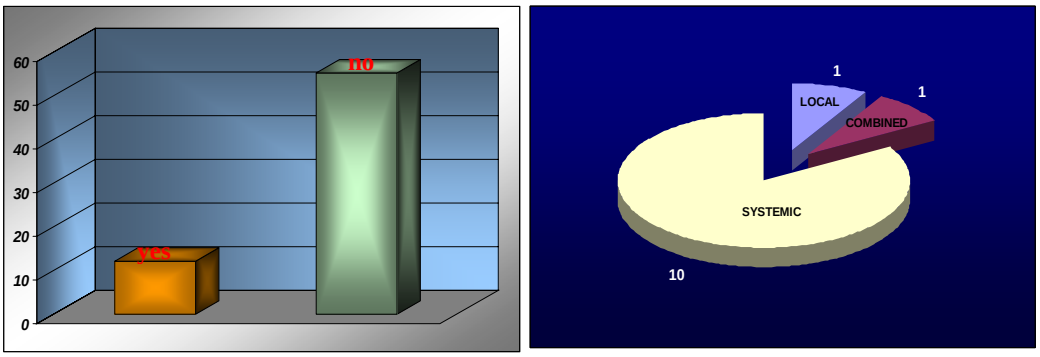
There was MVI in 13 (19%) cases of whom 12 (92%) developed recurrence**.** The incidence of MVI was more in symptomatic tumors and the recurrence was more in symptomatic tumors with MVI. Incidental tumors with MVI also developed higher recurrence pattern in our cases.



Recurrence

There was recurrence in 12 patients on follow up of whom 3 died from disease and 9 remained alive with disease.Only one patient developed local recurrence and all others developed systemic recurrence in lungs, bone and liver. One patient developed both local and systemic recurrence.Local recurrence was managed with resection and systemic recurrence by immunotherapy

RECURRENCE **RECURRENCE PATTERN**

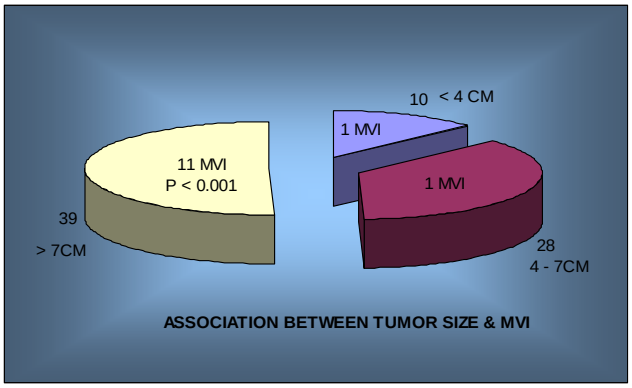


a) Recurrence in Symptomatic Patients

MVI occurred in 3 cases (14%) of incidentally detected tumors and in 10 cases (23%) of symptomatic tumors (p value < 0.001) .There was a significant increase in tumor recurrence for symptomatic tumors. In both the clinical presentations MVI was associated with recurrence (p value=0.008 for asymptomatic and <0.0001 for symptomatic patients).

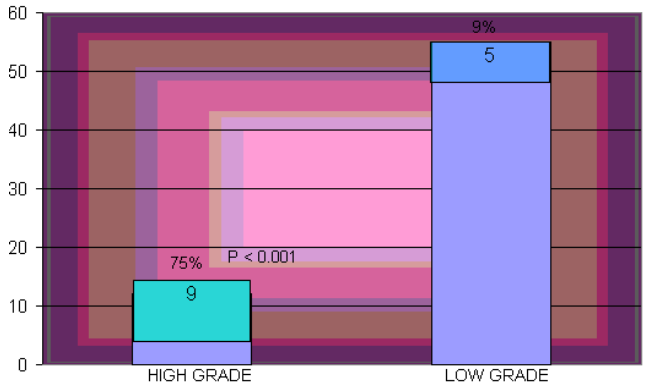
b) Recurrence in Relation to Tumour Size

Possible association between tumor size and MVI was analysed .In 10 tumors of < 4 cm size there was MVI in 1 case In 28 tumors of 4-7 cm there was MVI in 1 tumor.In 39 tumors of more than 7 cm size 12 had MVI with p value of < 0.001. Those who had MVI had higher recurrence.



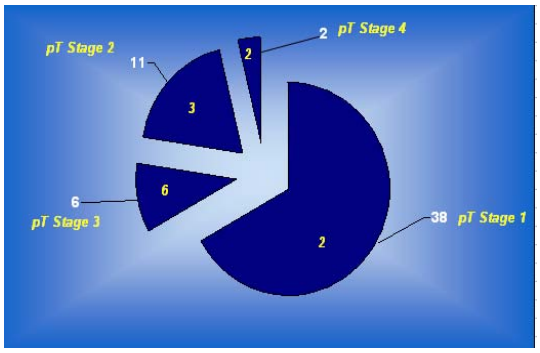
c) Recurrence and Tumour Grade

There was MVI in 9%(5/55) of the low grade tumors but 75%(9/12) of the high grade tumors had MVI (P<.000I). All high grade tumours with MVI had recurrence where as low grade tumours 66% had recurrence if MVI was present.

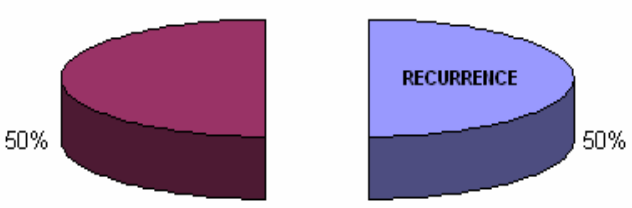


d) Recurrence and Tumour Stage

For pathological stage there was MVI in only 5% of patients with stage I. Pathological stage III and stage IV had an incidence of 100% with p value < .0001.



Further stratification of patients with stage 1 and 2 revealed that among those stage 1 no recurrence occurred for those without MVI .

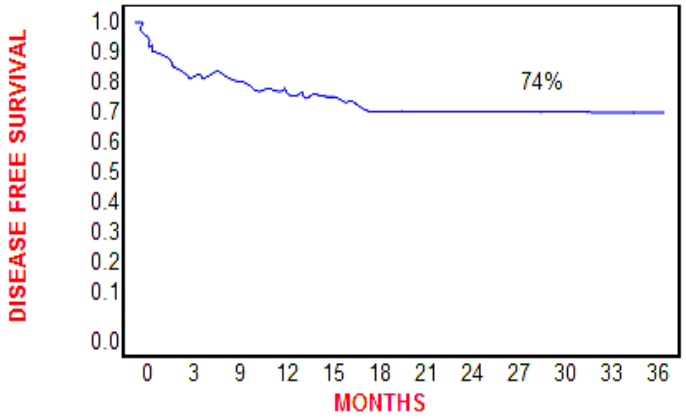


RECURRENCE IN PATHOLOGICAL STAGE-1 CASES WITH MVI

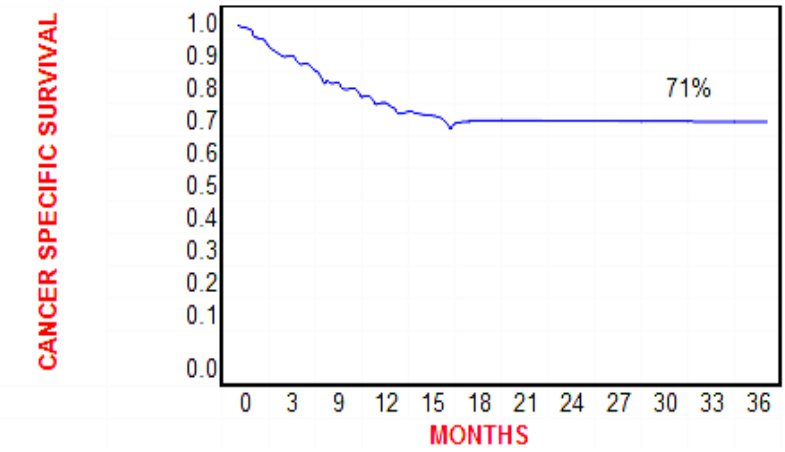
But the recurrence rate was about 50% for those with MVI (p<. 0001). In Stage 2 patients the recurrence rate was 100 % for with MVI. All Stage 3 and Stage4 patients with MVI had recurrences. Significance of MVI alone as a factor for recurrence is not available for analysis in high stage tumors

Survival Statistics

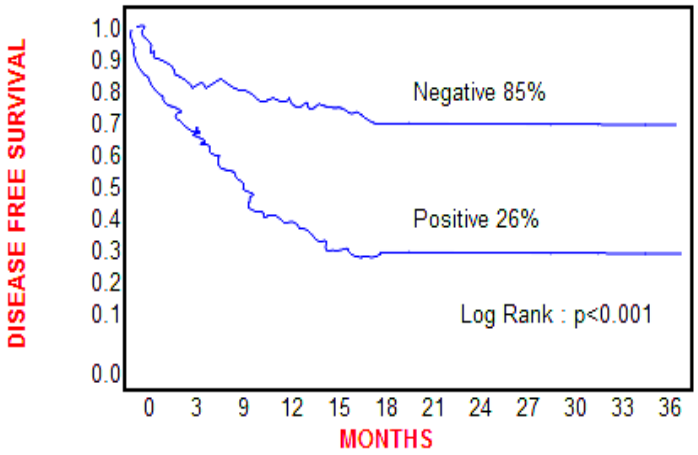
In our study we analysed the disease free survival and the cancer specific survival There was recurrence in 12 cases of which 3 died of the disease and the remaining cases were alive with the disease at the conclusion of the study.



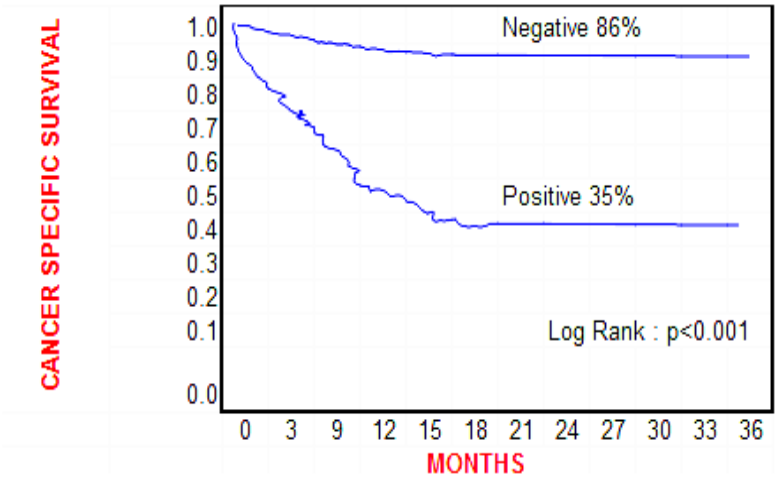
By looking at disease free survival curves the probability of disease free survival of all pts at 36 months was 74% over all. The disease free survival is affected by the recurrence of the disease.The probability of cancer specific survival was found to be 71 % for all patients in our study.



We also analysed the how the cancer specific survival and disease free survival was affected by the presence of microvascular invasion. By looking at disease free survival curves the probability of disease free survival of all pts at 36 months was 26% with MVI and it was 85% without MVI.



The probability of cancer specific survival was 35% with MVI and 86% without MVI. Cox regression analysis was used to compare the more important histological factor which revealed MVI was the most important prognostic factor.



DISCUSSION

Factors influencing the recurrence following radical nephrectomy in organ confined or locally advanced RCC are anatomical, histological, clinical and molecular.Clinical factors include patient performance status, localized symptoms, cachexia, anaemia, platelet count Anemia, thrombocytosis, hypercalcemia, albuminuria, elevated serum alkaline phosphatase erythrocyte sedimentation rate, and other para neoplastic signs or symptoms have also correlated with poor outcomes for patients with RCC

The aim of our study was to find out the significance of established prognostic variables determining the recurrence and the significance of micro vascular invasion .In our study the incidence of tumors was about three times more common in males correlating with literature incidence. The recurrence was not altered by the sex status which implies biological behaviour of the tumor is same in both the sexes.

In our study all patients had performance status of 0 or 1.There was no correlation between performance status and recurrence. Patients with good performance status withstood the radical procedure well. But the performance status at recurrence determined the treatment because

immuno therapy was indicated in patient with good performance status only.

Majority of our patients were in the age group of 60-70 yrs. Age as a factor has been found to be significant in many studies revealing younger age group has favourable prognosis and good out come. Age was not found to be a significant factor determining the recurrence in our study

The lab variables were analysed which revealed that except in few cases of anaemia no significant alteration in serum chemistry was seen. We did not find out any significance of these parameters. The incidence of paraneoplastic syndromes according to literature was 40%. But in our study non metastatic tumors did not have paraneoplastic syndromes but was found in metastatic tumors. The significance was not analysed because of non occurrence of paraneoplastic syndromes.

The incidental tumors were 22 and symptomatic tumors were 55 in our study.Symptomatic presentation was associated with greater tumour size and higher grade and higher incidence of MVI.Those patients with symptomatic presentation and MVI had higher recurrence rate when compared to those without MVI and incidental with or without MVI. The size of the tumors varied in our study with majority were more than 7

cm in size. Taking size into consideration tumor recurrence occurred in tumours more than 7 cm . Even in small tumors when they had MVI they had recurrence. So for varied tumor sizes the presence of microvascular invasion was found to be statistically significant factor.

Most of the tumours were pT2 and the grade was G2.In our study higher incidence of MVI was found in higher pathological stage. All T3 tumours had microvascular invasion and all G3 tumours had MVI.All the patients in this category developed recurrence.In pT1 tumours there was 50% recurrence for tumours with MVI.In pT2 tumours all patients developed recurrence if they had MVI.

The analysis of histological sub type revealed the clear cell was the commonest sub type and all the recurrences occurred in that except one case of Bellini duct carcinoma which developed recurrence. As per the literature chromophobe and papillary tumors were found to be of good prognosis . Since the number of cases of other histology was low in our study the statistical significance was not analysable There was one case of sarcomatoid histology which developed recurrence.

The incidence of lymph node involvement was in eight cases of which seven cases were microvascular invasion positive. The significance of lymph node positivity is these tumors had high recurrence and the

recurrence was due to higher pathological stage, higher grade and microvascular invasion present in these tumors. The significance of MVI in these cases is not known as they had high chance of recurrence even in the absence of microvascular invasion.

The incidence of necrosis varied in our cases and the statistical analysis did not reveal any significance. The presence of venous thrombi occurred in two cases which were managed by thrombectomy.There was no case of venous wall invasion which required venacavectomy. Recurrence was not altered by presence of venous thrombi in our study.

Adrenal invasion was seen in three cases which were by direct contiguous spread there was no statistical significance for this finding in our study. All the cases adrenalectomy was performed except in few cases which had a small tumor in lower pole and adrenal was normal by pre operative evaluation and intraoperatively.

So we analysed in our study the individual prognostic factors that influenced the recurrence and how the MVI increased the recurrence by combining with these factors and how much it increased the risk over these factors alone. Our study revealed for the size, pathological stage, grade the presence of MVI increased their influence on recurrence over their individual contribution

Recurrence was seen in 12 cases with 2 local recurrence and 10 as systemic recurrence. Out of the 12 cases 10 had MVI (83%). Haematogenous malignant dissemination relies on tumor access to microvasculature which alone confers on these tumors a higher risk of developing metastasis (**van poppel etal)** reported a 39% percentage rate of disease progression tumors with MVI and 6% without MVI.

In other study, Dekel **etal** reported similar findings ,with disease progression rates of 55.5 percentage for patients with MVI . The present results clearly shows that MVI is an important independent risk factor disease free survival [85 vs 26] and cancer specific survival [86 vs 35] for negative and positive MVI respectively.

Mrstik et al reported disease progression rate of 55.5% for pts with MVI. A study by **Marcos etal** in 230 patients revealed MVI in **59** patients of these 46 percentage developed recurrence . Among the 171 patients with no MVI only 11 developed recurrence. An association between MVI and the tumor size suggests its relationship with volumetric tumor growth. Even for patients with tumors less than 4cm and of low grade the presence of MVI should mandate a close follow-up as one patient has developed recurrence.

The incidence of MVI increased with pathological stage even in patients with stage 1and 2 incidence of MVI influenced the recurrence. So this finding should always be reported by pathologists and must be strongly considered when following up regimen of these patients .Our study showed that the presence of MVI in patients with RCC undergoing surgery suggests a more aggressive followup . This finding if validated by further studies might determine the use of adjuvant therapy

In our study the probability of cancer specific survival was 71 % for all patients with MVI it was 35% and without MVI it was 86%.The median survival at 3 yrs for patients whose tumor had no MVI was 95 percentage and statistically better than that of patients whose tumors had MVI[25 percentage] with a relative risk of death of 4.23. This was the most significant independent factor when compared with established clinical and histopathological variables.

CONCLUSION

We have found the significant variables for recurrence are size of tumor more than 7cm, pathological stage, lymph node positivity,tumor grade and microvascular invasion. Of all the variables micro vascular invasion proved to be the most important factor determining the recurrence**.** Patients with MVI should be closely followed or might be considered for trials of adjuvant therapy.

PATIENT PROFORMA

1. NAME:

2. SERIAL NUMBER:

3. AGE:

4. SEX:

5. CLINICAL PRESENTATION:

INCIDENTAL
LOCAL/SYSTEMIC SYMPTOMS

6. LAB VARIABLES:

ANAEMIA
SR CALCIUM
ESR
LFT

7.INVESTIGATIONS: **X-RAY CHEST, USG,CT/MRI ,**
BONE SCAN

8.SURGICAL PROCEDURE:

9.HISTOPATHOLOGICAL ASSESSMENT:

TUMOR SIZE
HISTOPATHOLOGICAL SUB TYPE
PATHOLOGICAL STAGE
MICROVASCULAR INVASION
NODAL STATUS
MARGIN STATUS

10.POST OP FOLLOW UP:

PHYSICAL EXAMINATION
LFT
X/RAY CHEST
USG/CT SCAN

EVERY 4MONTHS FOR 1ST YEAR

EVERY 6 MONTHS FOR 2ND YEAR

EVERY 12 MONTHSFROM 3RD YEAR

11.FOLLOW UP RESULT

MASTER CHART

S.NO	AGE	SEX	SYMP	SIZE (cm)	HPE	GRA	NEC	MVI	NOD	STAGE	ECOG	REC
1	**47**	M	I	5	CRCC	1	A	P	A	T1B	0	Y
2	**62**	M	L	10	CRCC	2	A	A	A	T2	1	-
3	72	F	L	8	CRCC	2	A	A	A	T1B	1	-
4	**62**	M	I	3	CRCC	1	A	A	A	T1A	1	-
5	**59**	M	I	7	CRCC	2	A	A	A	T1B	0	-
6	**48**	M	I	4	CRCC	1	A	P	A	T1A	0	-
7	**61**	M	L	8	CRCC	1	A	A	A	T2	0	-
8	**59**	F	I	6	PAP RCC	1	A	A	A	T1B	1	-
9	**60**	M	I	4	CRCC	1	A	A	A	T1A	1	-
10	**43**	F	L	16	CRCC	3	P	P	P	T3A	1	Y
11	**66**	M	L	14	CRCC	3	P	P	P	T3A	1	Y
12	72	M	L	10	CRCC	3	P	P	P	T3A	1	Y
13	**64**	M	L	5	PAP RCC	1	A	A	A	T1B	1	-
14	**48**	M	I	5	CRCC	1	A	A	A	T1B	1	-
15	**49**	F	L	10	CRCC	2	A	A	A	T2	0	-
16	**63**	M	I	5	CHR RCC	1	A	A	A	T1B	0	-
17	**57**	M	L	18	CRCC	3	A	P	P	T3A	0	Y
18	73	M	I	5	CRCC	1	A	A	A	T1B	1	-
19	**64**	M	L	20	CRCC	3	A	P	P	T3A	1	Y
20	**65**	F	L	6	CRCC	1	A	A	A	T1B	1	-
21	**69**	M	I	5	CRCC	1	A	A	A	T1B	1	-
22	**60**	M	I	2	CRCC	1	A	A	A	T1A	0	-
23	**57**	M	L	5	CRCC	1	A	A	A	T1B	0	-
24	**64**	M	I	8	CRCC	2	A	P	A	T2	0	Y
25	**46**	M	I	3	PAP RCC	1	A	A	A	T1A	1	-
26	**49**	F	L	8	CRCC	2	A	A	A	T2	1	-
27	**55**	M	L	8	CRCC	2	A	A	A	T2	1	-
28	**50**	M	L	9	CRCC	2	A	A	A	T2	1	-
29	**56**	M	L	6	CRCC	2	A	A	A	T1B	0	-
30	**68**	M	I	3	CRCC	1	A	A	A	T1A	1	-
31	**64**	M	L	10	CRCC	2	A	A	P	T3A	0	Y
32	**63**	F	L	8	CRCC	2	A	A	A	T2	1	-
33	**59**	M	L	5	CRCC	1	A	A	A	T1B	1	-
34	**59**	M	L	7	CRCC	1	A	A	A	T1B	1	-
35	**62**	F	L	8	CRCC	1	A	A	A	T2	0	-
36	72	M	L	8	CRCC	1	A	A	A	T2	1	-
37	73	M	L	8	CRCC	1	A	P	A	T2	0	-
38	**60**	M	L	5	CRCC	1	A	A	A	T1B	0	-
39	**61**	F	I	3	CRCC	1	A	A	A	T1A	1	-
40	**58**	M	I	2	CRCC	1	A	A	A	T1A	0	-
41	**49**	M	I	4	CRCC	1	A	A	A	T1A	1	-
42	**56**	M	L	9	PAP RCC	2	A	A	A	T2	0	-

43	**46**	M	L	10	CRCC	3	A	A	A	T2	1	-
44	73	M	L	7	CRCC	2	A	A	A	T1B	0	-
45	**62**	M	L	8	CRCC	2	A	A	A	T2	0	-
46	**63**	M	L	12	CRCC	3	A	P	A	T2	1	Y
47	**66**	M	L	8	CRCC	1	A	A	A	T2	1	-
48	**58**	M	L	8	PAP RCC	2	A	A	A	T2	1	-
49	**53**	M	I	3	CRCC	1	A	A	A	T1A	1	-
50	**54**	F	L	7	CRCC	2	A	A	A	T1B	1	-
51	**55**	F	L	8	CRCC	3	A	A	A	T2	1	Y
52	**60**	M	L	16	BELLINI	3	A	P	P	T3A	0	Y
53	**62**	M	L	9	CRCC	2	A	A	A	T2	1	-
54	**63**	F	L	9	CRCC	2	A	A	A	T2	1	-
55	**64**	M	L	10	CRCC	2	A	A	A	T2	1	-
56	**53**	M	L	11	CHR RCC	2	A	P	A	T2	1	-
57	**54**	M	L	8	CRCC	2	A	A	A	T2	1	-
58	**49**	M	I	8	CRCC	2	A	A	A	T2	1	-
59	**50**	M	L	14	CRCC	3	P	P	P	T3A	0	Y
60	72	M	L	10	CRCC	3	A	A	A	T2	1	-
61	73	M	I	8	CRCC	2	A	A	A	T2	1	-
62	74	M	L	10	CRCC	3	A	A	A	T2	1	-
63	**70**	M	L	8	CRCC	2	A	A	A	T2	1	-
64	**68**	M	L	8	CRCC	2	A	A	A	T2	0	-
65	**66**	M	I	7	CRCC	2	A	A	A	T1B	1	-
66	**64**	M	L	8	CRCC	2	A	A	A	T2	1	-
67	**68**	M	I	7	PAP RCC	2	A	A	A	T1B	1	-

ABBREVIATIONS

M-MALE

F- FEMALE

L – LOCAL SYMPTOMS

I – INCIDENTAL

CRCC – CLEAR CELL RENAL CELL CANCER

PAP RCC – PAPILLARY RCC

REC-RECURRENCE

MVI-MICROVASCULAR INVASION

GRD-GRADE

NEC-NECROSIS

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